

# Monoclonal Antibody-Based Therapies for Hematologic Malignancies

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**Purpose:** To review recent advances in the development and clinical roles of monoclonal antibody (MoAb)-based therapies in the treatment of hematologic malignancies.

**Design:** A search of MEDLINE and CANCERLIT was conducted to identify relevant publications. The bibliographies of these references also were used to identify articles and abstracts. These references were then reviewed.

**Results:** In the two decades since the first patient was treated with MoAb therapy, there have been significant advances in the biology, pharmacology, and clinical application of MoAb-based therapies. Three distinct fields of research have emerged: unconjugated MoAbs, immunotoxin-conjugated MoAbs (ITs), and radionuclide-conjugated MoAbs (RICs). The unconjugated MoAbs are less toxic but depend on host mechanisms to mediate

cytotoxicity. The ITs carry a potent toxin, although at the cost of a narrow therapeutic index that may limit clinical use. The RICs offer significant potency, even in refractory disease, but their complexity may limit their use to large cancer centers. The current challenges in the development of MoAb-based therapies are to identify the proper target antigens, contend with bulk disease in which penetration may be limited, and choose the optimal clinical settings for their use, such as the minimal residual disease state or in combination with conventional chemotherapy.

**Conclusion:** Although significant research is still needed, MoAb-based therapies promise to offer new options for the treatment of patients with hematologic malignancies.

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PATIENTS WITH hematologic malignancies have benefited most from the advances in cancer treatment over the past several decades. Although modern therapies have increased remission rates, most patients still ultimately succumb to their disease. The barriers to cure include tumor-cell resistance and the unacceptable toxicity of available treatments, which limit optimal cytotoxic dosing and make these therapies unavailable to debilitated or older patients. Even the success in such diseases as Hodgkin's disease has been tainted by the alarming rate of malignant and nonmalignant sequelae of therapy in these otherwise cured patients. The challenge remains to develop less toxic, but more effective, targeted therapies.

The idea of recruiting antibodies to the fight against cancer dates at least to 1953, when Pressman and Korngold<sup>1</sup> showed that antibodies could specifically target tumor cells. Not until the 1975 publication by Kohler and Milstein,<sup>2</sup> however, in which they described their Nobel prize-winning work in hybridoma technology, did a continuous supply of monoclonal antibodies (MoAbs) that targeted prespecified antigens become available. By 1979, Nadler et al<sup>3</sup> treated the first patient with MoAb therapy. Since then, more than 2,000 cancer patients have received MoAb serotherapy. The present review will describe the development of these exciting agents and consider the present and potential roles for MoAbs in the treatment of hematologic malignancies. Although MoAbs also are used in the purging of autologous stem cells ex vivo and in the treatment of graft-versus-host

disease, these topics have been extensively reviewed elsewhere<sup>4,5</sup> and will not be examined here.

In general, three main classes of cytotoxic MoAbs have been developed. The first consists of unconjugated MoAbs, in which the MoAb itself mediates cell death. The other two classes are composed of MoAbs conjugated either to a potent toxin or a radioisotope. Despite the simplicity of the concept, researchers have confronted a number of technical difficulties, which include the selection of a proper target antigen, efficient delivery of the MoAb to that target, complete eradication of tumor at all sites of disease, and the attendant toxicities of the MoAb therapy itself.

The selection of a proper target antigen is essential because it cannot also be shared by critical host tissues. Fortunately, hematologic malignancies express some antigens not shared by other crucial organs, although typically they are shared by one or more normal lymphoid and/or myeloid cell compartments. Cross-reactivity with normal host cells is tolerable as long as the progenitor or stem-cell

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population remains intact and can regenerate the normal hematologic tissue.

The target antigen must also be present either on all neoplastic cells or on the self-renewing clonogenic population of neoplastic cells. Furthermore, target antigen expression must persist despite the strong negative selection applied by MoAb therapies. Malignant disease may escape therapy if an antigen-negative clone develops, a problem encountered in some of the earlier trials that used anti-idiotypic MoAbs to treat patients with non-Hodgkin's lymphoma (NHL).<sup>6,7</sup> Radioimmunoconjugates (RICs) are an exception to this requirement because the radioisotope emits particles with enough energy to kill adjacent, potentially nonantigen-bearing cells.

Appropriate target antigens also must respond properly after they bind the MoAb. In the case of unconjugated MoAbs, the antigen-MoAb complex cannot undergo internalization or shedding, but rather must remain on the cell surface to allow the exposed constant portion (Fc) to activate host effector mechanisms. In contrast, MoAb-toxin conjugates (immunotoxins [ITs]) must be internalized, which allows the toxin access to critical intracellular processes. MoAb-radioisotope conjugates (RICs) vary in their antigen-modulation requirements, which depend on the specific radioisotope used. Antigen density and MoAb binding affinity also influence MoAb cytotoxic efficacy.<sup>8,9</sup>

The MoAb must have access to tumor cells at all sites of disease. Bulky tumors with poorly vascularized centers and high interstitial pressures may hamper MoAb diffusion.<sup>10-12</sup> Moreover, lymphomatous nodes may have disproportionately poor capillary permeability, which further limits MoAb penetration.<sup>13</sup> MoAb fragments (Fab' fragments) and smaller 25-kd, single-chain, antigen-binding proteins have the potential to penetrate deeper and more rapidly into tumor masses.<sup>14,15</sup> Unfortunately, the serum half-life of these agents appears to be shortened, which lowers the mean serum concentration and decreases the concentration gradient that drives diffusion into the tissue sites.<sup>16</sup>

Circulating tumor cells pose different problems. Most trials that include patients with peripheral-blood involvement show rapid clearance of circulating malignant cells.<sup>17-19</sup> Unfortunately, these responses are usually transient because the collective bulk of circulating disease acts as a sink for the MoAb, which leads to its rapid clearance from the circulation.<sup>19,20</sup> Circulating free antigen presents an analogous problem.<sup>21</sup>

Once the MoAb reaches the tumor cell, it must cause cell death. The MoAb may trigger complement-dependent cytotoxicity (CDC)<sup>22</sup> or antibody-dependent cell-mediated cytotoxicity (ADCC). Murine MoAbs are less effective than

human MoAbs at mediating such host effector mechanisms. Accumulating evidence also points to direct MoAb cytotoxic effects on tumor cells.<sup>23,24</sup> For example, the MoAb may block binding of an endogenous ligand, which deprives the cell of a critical survival signal,<sup>25</sup> or it may mimic it, which triggers cytotoxicity or growth arrest.<sup>26,27</sup>

Thus, the properties of the target antigen, the MoAb, and their interaction *in vivo* determine the activity of a given MoAb therapy. The final determinant of success is the degree of nonspecific toxicity attributable to the MoAb. The side-effect profile of MoAb therapies varies considerably, depending on whether the MoAb is conjugated and the nature of the conjugated moiety. Because these agents are foreign proteins, acute allergic reactions are common. Approximately one third of the patients experience infusion-related symptoms, which include fevers, rigors, and diaphoresis in approximately 20% and hypersensitivity reactions, such as urticaria, pruritis, and bronchospasm, in approximately 20%.<sup>28</sup> Rarely, anaphylaxis develops.

Toxicity also may result from the MoAb cross-reacting with normal host tissues. Many MoAbs directed against hematologic malignancies deplete a subset of lymphoid or myeloid cells. Another consequence of the administration of xenogenic MoAbs is a host humoral response, specifically the formation of human antimouse antibodies (HAMA). With ITs, a separate humoral response to the toxin conjugate also may develop. Approximately one third of the patients will develop a HAMA response. Even profoundly immunosuppressed patients, such as those after bone marrow transplantation<sup>29,30</sup> or with advanced HIV disease,<sup>31</sup> can form HAMA responses. These host responses may substantially alter the pharmacokinetics of the MoAb if re-administered, which leads to rapid clearance from the circulation and limits the ability to re-treat patients.<sup>32,33</sup> The theoretical possibility of inducing serum sickness also exists.

Techniques to humanize murine MoAbs have been developed to ameliorate the host humoral response. Through genetic engineering methods, the murine variable regions responsible for antigen recognition can be spliced into a human immunoglobulin (Ig) backbone,<sup>34</sup> which creates a chimeric protein with a prolonged serum circulation time and substantially less immunogenicity,<sup>35-37</sup> which allows repeated dosing.<sup>38-41</sup> The human Fc portion of a chimeric MoAb also improves its ability to mediate CDC and ADCC, which increases potency compared with the parent murine MoAb.<sup>39,42-44</sup> Acute infusion-related toxicities appear to be identical to those seen with murine MoAbs<sup>38,41,45</sup> but decrease substantially with second and subsequent doses.<sup>46</sup>

## UNCONJUGATED MOABS

Unconjugated MoAbs constitute the simplest application of targeted MoAb therapy. Table 1 lists the major clinical trials of unconjugated MoAbs in hematologic malignancies. Despite early limited successes,<sup>3</sup> a number of barriers to its effective use had to be overcome. Early attempts to choose target antigens focused on maximizing selectivity. In the case of surface Ig-expressing B-cell malignancies, the idiotype of the Ig molecule represents a unique tumor-specific cell-surface antigen and, thus, a logical target for MoAb therapy.<sup>74</sup>

A series of trials in a total of 34 patients with NHL used a broad range of doses of anti-idiotypic MoAbs and documented clinical responses in 23 patients with six complete responses (CRs),<sup>6,48,75,76</sup> five of which lasted more than 5 years.<sup>77</sup> Biopsy specimens of tumor and bone marrow showed antibody binding, which proved that these large molecules could penetrate into tumor-involved tissues.<sup>48</sup> Unfortunately, relapses with idiotype-negative tumor resulted in tumor escape from therapy.<sup>7,49,78,79</sup> The presence of circulating shed idiotype<sup>48,80</sup> and the formation of HAMA responses further limited efficacy.<sup>33,48</sup> Finally, the need to custom make anti-idiotypic MoAbs based on each patient's tumor made this specific therapy untenable. Because of these difficulties, anti-idiotypic therapy has been largely abandoned. Current approaches target hematopoietic, sometimes lineage-specific, antigens that are common to all tumors of a given subtype, such as B-cell NHL or T-cell acute lymphoblastic leukemia (ALL). The trade-off is that normal host cells that express these antigens also are targeted, which contributes to the toxicity profile of these otherwise well-tolerated agents.

All the trials published to date have been phase I or II studies that used a broad range of doses and schedules with widely varying efficacy rates (Table 1). The anti-CD20 MoAb, Rituxan (IDEC Pharmaceuticals, San Diego, CA, and Genentech, Inc, San Francisco, CA), has been the most extensively studied unconjugated MoAb. This murine-human chimeric MoAb consists of the murine variable regions from the parent 2B8 MoAb grafted onto a human IgG1 constant-region backbone.<sup>43</sup> The CD20 antigen is nearly an ideal target for unconjugated MoAb therapy because it is not expressed on precursor B cells or stem cells, but is found in high density on mature B cells (normal and malignant), with the exception of plasma cells.<sup>81</sup> The antigen is not shed and does not appear to undergo modulation in response to antibody binding. Furthermore, *in vitro* data suggest that MoAb binding to CD20 may trigger apoptosis<sup>27</sup> and thereby decrease reliance on host CDC or ADCC.

The initial phase I trials, which used a single bolus dose

and repeated weekly dosing in patients with relapsed CD20+ B-cell NHL, were stopped before the dose-limiting toxicity (DLT) was reached, despite the administration of more than a gram of MoAb to some patients,<sup>41,62</sup> which attested to the benign side-effect profile of this particular MoAb. Subsequent phase II trials enrolled more than 200 patients with relapsed low-grade and follicular NHL.<sup>46,63</sup> The patients received 375 mg/m<sup>2</sup> of Rituxan weekly for 4 weeks. Although these patients had a median of two prior relapses, the response rate was 48%, with 6% CRs. Many patients had no detectable residual disease within peripheral-blood and bone marrow compartments, based on polymerase chain reaction (PCR) analysis for the t(14;18) translocation, although patients still had nodal involvement.<sup>62</sup> The median time to response was approximately 2 months, with some patients who continued to show progressive responses for several months thereafter.

Toxicities were generally minor and consisted almost entirely of acute infusion-related reactions. As expected, the normal mature B-cell population rapidly declined after treatment and recovered over 3 to 9 months. There was no increase in the rate of infections, probably because Ig and T-cell levels remained stable. Finally, only minimal HAMA responses were documented in less than 1% of the patients. Based on these data, the Food and Drug Administration approved the regimen of 375 mg/m<sup>2</sup> weekly for 4 weeks for the treatment of relapsed low-grade or follicular NHL.

Preliminary data are available on the use of Rituxan in conjunction with combination chemotherapy. *In vitro* studies showed synergistic cytotoxicity when CD20+ cell lines were treated with Rituxan followed by chemotherapy.<sup>83,84</sup> One provocative study treated 38 patients with low-grade NHL (31 patients were previously untreated) with Rituxan in combination with full-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy (M. Czuczman, personal communication, March 1998). The response rate was 100%, with about two thirds CRs. Furthermore, of eight patients who had detectable disease in peripheral blood and bone marrow, based on PCR analysis for t(14;18), seven patients achieved a clinical CR and became PCR-negative in the blood and bone marrow, an unusual occurrence for patients treated with chemotherapy alone.<sup>85</sup> To date, one of these patients has become PCR+ for t(14;18), although he remains in a clinical CR. Follow-up data are still too immature to determine whether Rituxan, either alone or in combination, will affect the natural history of low-grade NHL.

Rituxan also has been used to treat small numbers of patients with intermediate-grade (aggressive) NHL. A phase II study of 54 patients with relapsed or refractory intermedi-

Table 1. Major Studies of Unconjugated MoAbs

Disease	Target Antigen	MoAb	No.	Total Dose	Schedule	Outcome*	HAMA	Reference
B cell								
B-NHL, relapsed	Unknown	Ab89	1	250 mg	IV over 5 hours	Transient decrease in circulating cells	NA	3
B-NHL, relapsed	Ig idiotype	Anti-Id ± IFNα or pulse CHL	40	400 mg-15.5 g	IV over 4 hours	4 CR, 22 PR (many of short duration)	6/27	6, 47-49
B-NHL, relapsed	CD21	ORB7	18	0.1-40 mg (trace labeled with <sup>125</sup> I)	IV over 60 minutes	No responses	5/18	50
B-cell NHL/CLL/ALL, majority relapsed	CD52	CAMPATH-1H ± -1G (rat MoAb)	20	50-875 mg	IV over 3 hours	1 CR, all patients showed decrease in circulating tumor cells	2/18	51
B-NHL	CD52	CAMPATH-1H (rat/hu chimeric)	2	85-126 mg	IV over 2-4 hours	2 PR	0/2	40
CLL, previously untreated	CD52	CAMPATH-1H	9	30 mg 3 × week × 18 weeks	IV (5 patients) or SC (4 patients)	3 CR, 5 PR (CLL cells cleared from PB in all patients and from BM in 7)	NA	52
CLL, relapsed	CD52	CAMPATH-1H	29	30 mg 3 × week × 12 weeks	IV over 2 hours	1 CR, 11 PR (CLL cells cleared from PB in 28, BM in 10)	NA	53
CLL/PCL, relapsed	CD52	CAMPATH-1H	7	30 mg 3 × week × 6-12 weeks	SC	1 CR (PCL), 3 PR (CLL)	NA	54
CLL, relapsed	CD52	CAMPATH-1H	10	30 mg 3 × week × 6 weeks	SC	5 CR, 2 PR of 8 assessable	NA	55
B-NHL, relapsed	CD19	CLB-CD19 ± rIL-2	13 (7 with rIL-2)	225-1,000 mg total dose with continuous IV rIL-2	IV over 4 hours × 4 days or twice weekly × 12 weeks	1 PR (brief) without rIL-2 and 1 PR with rIL-2	0	56, 57
ALL, relapsed	CD10	J5	4	13.5-425 mg over 3-8 infusions	IV over 15 minutes to 4 hours	3 Patients with decrease in circulating blasts	NA	17
CLL, relapsed	CD5	T101	13	1-140 mg per dose	2-50 hours	Transient decrease in circulating cells	0/13	58
CLL, relapsed	CD5	T101	6	10-500 mg per dose	24-hour continuous IV, 1 to 8 treatments every 1 to 4 weeks	2 Patients with transient decrease in circulating cells	0/6	59
B-NHL, refractory	HLA-DR	LYM-1	10	58-465 mg per dose	IV, weekly × 4	No responses	0	60
B-NHL, refractory	CD20	1F5	4	52.4 mg-2.38 g	Continuous IV over 5 to 10 days	1 PR lasting 6 weeks	1/4	61
B-NHL, low-grade, relapsed	CD20	IDEC-C2B8	15	10-500 mg/m <sup>2</sup>	IV bolus	2 PR of 15 assessable	0	45
B-NHL, relapsed	CD20	IDEC-C2B8	20	125-375 mg/m <sup>2</sup> weekly for 4 weeks	IV bolus	6 PR, 5 MR of 18 assessable, including 4 of 6 patients with bulky disease	0	62
B-NHL, low-grade, relapsed	CD20	IDEC-C2B8	203	375 mg/m <sup>2</sup> weekly × 4 weeks	IV bolus	50% CR + PR	1	46, 63

B-NHL, intermediate- or high-grade, relapsed	CD20	IDEC-C2B8	54	375 mg/m <sup>2</sup> weekly × 8 weeks or 375 mg/m <sup>2</sup> × 1 followed by 500 mg/m <sup>2</sup> × 7 weeks	IV bolus	4 CR, 11 PR of 47 assessable, median time to maximal response was 9 weeks	NA	64
B-NHL, low-grade, relapsed	CD20	IDEC-C2B8	38	375 mg/m <sup>2</sup> × 6	IV bolus	67% CR, 33% PR, 7 of 8 patients converted to PCR-negative in PB and BM after treatment	0	65
B-NHL, low-grade, relapsed	CD20	IDEC-C2B8	31	375 mg/m <sup>2</sup> weeks 5-8 + IFN- $\alpha$ 5 MU/m <sup>2</sup> 3 × week × 3 months	IV bolus	2 CR, 13 PR of 26 assessable	0	66
B-NHL, intermediate- or high-grade, previously untreated	CD20	IDEC-C2B8	33	375 mg/m <sup>2</sup> + CHOP × 6	IV bolus	24 CR, 8 PR	NA	67
T Cell								
T-NHL, relapsed	CD5	Anti-Leu-1	7	13-761 mg, over 4 to 17 treatments	IV over 4-6 hours	4 PR	4/7	33
CTCL, both previously untreated and relapsed	CD5	T101	10	10-500 mg per dose	24-hour continuous IV, 1 to 8 treatments every 1 to 4 weeks	4 Patients with transient decrease in circulating cells	5/10	59
T-ALL, both previously untreated and relapsed	CD25	Anti-TAC	19	100-490 mg	IV over 5-445 days	2 CR, 4 PR, remissions lasted from 9 weeks to > 3 years	3/19	25, 68
CTCL, relapsed	CD4	OKT412	15	10-80 mg twice weekly × 3 weeks or 50-200 mg 30 mg 3 times weekly × 12 weeks	IV bolus	6 PR	4/15, 1 of low titer	69, 70
PLL, relapsed	CD52	CAMPATH-1H	15		IV over 2 hours	9 CR, 2 PR	0	71
Myeloid AML	CD14, CD15, and others	PMN 6, PMN 29, PM-81, AML-2-23	3	170-660 mg	IV over 8 hours to 7 days	3 Patients with transient decrease in circulating blasts	1/3	72
AML	CD33	M195	10	6-76 mg (trace labeled with <sup>111</sup> In)	IV over 20 minutes daily × 4-6 days	2 Patients with transient decrease in circulating blasts	4/6	73
AML, relapsed	CD33	Hu-M195	13	0.5-10 mg/m <sup>2</sup> × 6 doses over 18 days (one dose trace labeled with <sup>111</sup> In) up to 216 mg	IV over 20 minutes every 72 to 96 hours	No responses	0	38

Abbreviations: CR, complete response; PR, partial response; NA, not available; IFN- $\alpha$ , interferon alpha; CHL, chlorambucil; rIL-2, recombinant interleukin-2; PB, peripheral blood; BM, bone marrow; CTCL, cutaneous T-cell lymphoma; IV, intravenous; SC, subcutaneous; hu, humanized; MU, million units.

\*Only complete and partial responses are reported.

ate- or high-grade NHL, which included 12 patients with mantle cell lymphoma (MCL), showed a 32% single-agent response rate.<sup>64</sup> Three responses were in the 11 assessable MCL patients. A trial of CHOP and Rituxan has also been conducted in 33 patients (27% aged older than 65 years) with previously untreated intermediate-grade NHL, 73% of whom had stage III or IV disease. This combination resulted in a response rate of 97%, with 73% CRs.<sup>67</sup> The study also showed that the two modalities could be administered together safely without increased toxicity. Rituxan is currently being tested in other B-cell malignancies, which include chronic lymphocytic leukemia (CLL), MCL, and multiple myeloma. In the latter case, although plasma cells do not express CD20, there is some evidence that the clonogenic precursor may.<sup>66</sup> Large cooperative group trials are addressing the use of Rituxan as an adjuvant therapy for patients with intermediate-grade NHL. Maintenance therapy is also being explored,<sup>67</sup> although antigen escape may limit its use.<sup>68</sup>

Another MoAb that has undergone evaluation is the CAMPATH-1 MoAb, targeted against CD52, an antigen expressed by both B and T cells, as well as monocytes and granulocytes, but not stem cells.<sup>69</sup> Early studies used a broad range of multiple bolus doses of rat monoclonal IgM or IgG to treat 20 patients with a range of B-cell malignancies, which included NHL, CLL, and ALL.<sup>51</sup> The IgG depleted malignant cells from blood, bone marrow, and spleen but had no appreciable effect on lymph nodes or extranodal sites of disease. Toxicities were mostly infusion related, such as fever, rigors, malaise, nausea, and vomiting, as well as bronchospasm and angioedema in a few patients.

The humanized version, CAMPATH-1H, has shown efficacy in CLL, although with significant toxicity. A series of studies in patients with previously untreated or refractory CLL that used a fixed dose of 30 mg three times weekly either intravenously or subcutaneously for 6 to 18 weeks documented response rates that ranged from 42% to greater than 80% and a 12-month median duration of response.<sup>52-55</sup> Again, lymph nodes were the most resistant sites of disease,<sup>55</sup> which argued for poor penetration of CAMPATH-1H. Toxicities consisted of infusion-related reactions, World Health Organization grade IV neutropenia or thrombocytopenia of short duration in some patients, and grade IV lymphopenia in all patients, which led to profound immunosuppression. CD4 counts remained depressed for months in some patients,<sup>60</sup> and there were multiple cases of opportunistic infections, mostly viral reactivation.<sup>91</sup> A separate study in 15 patients with T-cell prolymphocytic leukemia (PLL) also showed a CR in nine patients.<sup>71</sup> Unfortunately, two patients developed bone marrow aplasia; one patient died as a result. These aplastic events argue that although CD52 may not be

identifiable on early stem cells, a progenitor population may be depleted after treatment with the CAMPATH MoAb. In summary, despite evidence of activity in CLL/PLL, the CAMPATH-1H MoAb underscores the impact that antigen choice and cross-reactivity with normal tissues has on toxicity. Pivotal trials are in progress to secure approval in the United States for the use of CAMPATH-1H to treat refractory CLL.

MoAbs targeted against CD19,<sup>56,57</sup> CD21,<sup>50</sup> and HLA-DR<sup>60</sup> also have been tested in patients with B-cell NHL with limited success (Table 1). The CD19 and CD22 antigens are known to internalize on antibody binding, which makes them poor targets for unconjugated MoAb therapy.<sup>92</sup> Minor, transient responses also have been observed with the T101 MoAb, which targets CD5, a T-cell antigen expressed by CLL cells.<sup>58,59</sup> Studies showed that CD5 undergoes rapid modulation in response to T101 therapy. Other target antigens include CD30 for the treatment of anaplastic large-cell NHL<sup>93</sup> and CD40 for B-cell malignancies.<sup>26</sup>

CD10 and CD25 have been exploited as targets for the therapy of ALL. The former, also termed the common ALL antigen (CALLA), is expressed by a large proportion of ALL cells. An early phase I trial with the anti-CALLA J5 MoAb in four patients resulted in an immediate and rapid decrease in circulating blasts. Unfortunately, a population of CALLA blasts persisted, and as serum levels of J5 waned, CALLA+ blasts re-emerged.<sup>17,94</sup> In studies with the anti-Tac MoAb, which recognizes the interleukin-2 (IL-2) receptor, some patients experienced CRs that lasted up to 3 years.<sup>25,68</sup> T-cell depletion, however, resulted in several immunosuppression-related complications.

Finally, a number of studies have used unconjugated MoAbs to treat patients with cutaneous T-cell lymphoma. The T101 MoAb again was unimpressive in a phase I study of 10 patients who received a 24-hour intravenous infusion.<sup>59</sup> More significant, but short-lived, responses were seen with the cMT412 chimeric MoAb, targeted against CD4, another T-cell restricted antigen.<sup>69,70</sup> Skin lesions responded in most patients, and cMT412 was shown on skin biopsy specimens. Although CD4 counts were depressed at the higher doses, the rate of opportunistic infections did not increase.

There is only limited published experience in the use of unconjugated MoAbs in the treatment of acute myelogenous leukemia (AML). A cocktail of IgM and IgG MoAbs selected for their ability to recognize granulocytes and/or monocytes was used to treat three patients with AML and resulted in only transient decreases in circulating blasts.<sup>72</sup> An unconjugated anti-CD33 MoAb was studied in 10 patients with AML, again with limited responses in two patients.<sup>73</sup>

Thus, unconjugated MoAbs continue to hold significant promise for the treatment of hematologic malignancies. The body of research to date identifies the importance of such issues as antigen modulation, host cross-reactivity, and tumor bulk in the efficacy and safety of these agents. The CD20 antigen appears to be one suitable target, and further studies with Rituxan will help delineate its ultimate place in the treatment of a variety of B-cell malignancies. As this field expands, the goal is to create an armamentarium of unconjugated MoAbs capable of treating every hematologic malignancy.

### IMMUNOTOXINS

An alternative to identifying MoAbs with both specificity and cytotoxicity has been the development of ITs. These constructs involve the linkage of the MoAb to a protein toxin, which allows the targeting and cytotoxic functions to be divided between the two moieties,<sup>95-99</sup> although ADCC may still contribute to overall IT cytotoxicity.<sup>100</sup> Growth factors and other natural ligands, such as IL-2, also can be used to carry toxins.<sup>101-105</sup> The toxins used (eg, ricin, diphtheria toxin [DT]) are highly potent natural products that disrupt protein synthesis at picomolar concentrations.<sup>106</sup> These IT constructs are at least three orders of magnitude more potent than unconjugated MoAbs *in vitro*, which show clinical responses at milligram doses.<sup>18,106</sup>

Unlike unconjugated MoAbs, which require the antigen-MoAb complex to remain on the cell surface, most ITs must be internalized after antigen binding to allow the toxin access to the cytosol.<sup>107,108</sup> Once inside, intracellular protein trafficking mechanisms must convey the toxin to the ribosomal complex.<sup>95</sup>

Plants and bacteria have been the source of most of the toxins studied. Ricin is a two-chain plant toxin that has been studied extensively in the treatment of hematologic malignancies.<sup>109-113</sup> DT, the only bacterial toxin used to date in the treatment of hematologic malignancies, also disrupts protein synthesis.<sup>114</sup> Although the conjugation of toxin to MoAb confers some target specificity, the binding domains of the toxins continue to mediate nonspecific binding to normal host tissues. Thus, the structure of the native toxin must be modified to delete the binding properties while cytotoxic activity is preserved. The simplest solution is to eliminate the binding domain.<sup>115,116</sup> Examples of such ITs include the ricin-based RFB4-dgA, directed against the CD22 antigen for the treatment of B-cell lymphomas,<sup>20</sup> and anti-T101-RTA, for the treatment of CLL.<sup>117</sup> Without the binding properties of the native toxin, these ITs rely on the internalization of the target antigen to achieve cytotoxicity, which thereby limits the choice of exploitable IT targets. An alternative strategy involves retaining the binding domain

but with modifications to limit nonspecific binding, which has been used with both ricin- and DT-based ITs.<sup>118,119</sup>

An alternative approach to IT development has been to fuse the DNA sequences that encode a toxin to the DNA elements that encode the antigen-recognition site (Fv) of the MoAb, which creates a relatively small molecule with both binding and cytotoxic properties.<sup>120-122</sup> The DAB<sub>486</sub>IL-2 and DAB<sub>389</sub>IL-2 fusion toxins embody this approach, in which DNA sequences for IL-2 replace domain 1 of DT.<sup>103,123</sup> Although these smaller molecules may have better penetration into bulky tumors and reduced immunogenicity,<sup>124</sup> they have lower binding affinities and may be less potent than whole MoAb conjugates.<sup>125</sup>

The vast majority of human trials of IT therapy have been phase I studies, designed to determine the maximum-tolerated dose and DLT (Table 2). Collectively, these trials have shown that therapeutic serum levels of IT, capable of up to a 5-log tumor cell cytoreduction based on preclinical data, can be achieved in humans with tolerable systemic and organ-specific toxicities. Both bolus dosing<sup>18,20</sup> and continuous infusion schedules<sup>19,126</sup> have been tested with no demonstrable advantage to continuous infusion.

A striking feature of the IT trials is the relatively uniform toxicities seen, despite the broad variation in MoAbs and toxins used. Most phase I studies were dose limited by the development of a vascular leak syndrome, characterized by features that included hypoalbuminemia, weight gain, peripheral edema, pulmonary edema, hypotension, and pericardial effusions.<sup>18,19,103,124,126,127,138,141</sup> Toxin-mediated endothelial injury has been implicated as the cause of this reaction.<sup>146</sup> Other common side effects include fever, malaise, nausea, and hypersensitivity reactions (attributable to the murine origin of ITs). Reversible transaminase level elevations are seen frequently, particularly with anti-B4-blocked ricin (bR)<sup>18,19</sup> and DAB<sub>486</sub>IL-2.<sup>102,103,134</sup> The dgA-ITs have been associated with rhabdomyolysis and CNS toxicities.<sup>20,124,126</sup>

Another common finding among IT trials is the high rate of host humoral responses to either the MoAb or toxin component. Re-treatment is not feasible in most patients who develop an HAMA or antitoxin response, because the IT is rapidly cleared from the serum and can be neutralized by the host antibodies. However, studies with the DAB<sub>486</sub>IL-2<sup>133</sup> and DAB<sub>389</sub>IL-2 fusion toxins<sup>143</sup> showed clinical efficacy despite the presence of detectable HAMA and anti-DT titers, which implied that not all humoral responses are neutralizing.

Table 2 lists the major published clinical trials of IT therapy, grouped by disease category. The trials in patients with NHL that used ITs composed of either anti-CD19 (anti-B4-bR<sup>18,19</sup> and HD37-dgA<sup>127,128</sup>) or anti-CD22 (RFB4-dgA<sup>20,124,126</sup>) MoAbs, uniformly showed low response rates

Table 2. Major Studies of Immunotoxins

Disease	Target Antigen	IT	No.	Schedule	MTD	Toxicity	HAMA/HARA	Response*	Reference
<b>B Cell</b>									
B-NHL, relapsed	CD22	Fab' RFBA-dgA	15	IV over 4 hours every 48 hours × 2 to 6 doses	75 mg/m <sup>2</sup>	Fever, myalgias, transient aphasia, rhinodomyolysis, VLS	4/14	5 PR, lasting 1 to 4 months	124
B-NHL, relapsed	CD22	IgG-RFB4-dgA	26	IV over 4 hours every 48 hours × 2 to 12 doses	26-40 mg/m <sup>2</sup> total dose	Fever, myalgias, transient aphasia, rhinodomyolysis, VLS	9/24	1 CR, 5 PR, transient, of 24 assessable	20
B-NHL, relapsed	CD22	IgG-RFB4-dgA	18	Continuous IV for 8 days	19.2 mg/m <sup>2</sup> /8 days	VLS, aphasia, hypotension	6/16	4 PR	126
B-NHL, relapsed	CD19	IgG-HD37-dgA	23	IV bolus every 48 hours × 4	16 mg/m <sup>2</sup> /8 days	VLS, acrocyanosis	5/15	1 CR, 1 PR	127
B-NHL, relapsed	CD19	IgG-HD37-dgA	10	Continuous IV for 8 days	19.2 mg/m <sup>2</sup> /8 days	VLS, acrocyanosis	2/8	1 PR of 9 assessable	127
B-NHL, relapsed	CD19	IgG-HD37-dgA	8	IV bolus over 1 hour every 4 hours × 4	8 mg/m <sup>2</sup>	VLS, orthostatic hypotension, rhinodomyolysis	2/7	1 PR before death at day 8	128
B-cell neoplasms	CD19	Anti-B4-bR	25	IV over 1 hour daily × 5 days	250 µg/kg	Transaminase elevations, thrombocytopenia, fever, fatigue, VLS	9/25	1 CR, 2 PR	18
B-cell neoplasms	CD19	Anti-B4-bR	34	Continuous IV × 7 days	350 µg/kg	Transaminase elevations, thrombocytopenia, dyspnea, fever, VLS	24/34	2 CR, 3 PR	19
B-NHL phase I adjuvant post-ABMT	CD19	Anti-B4-bR	12	Continuous IV × 7 days	280 µg/kg	Transaminase elevations, thrombocytopenia, dyspnea, fever, VLS	7/12	7 relapse-free, median F/U 4 years	30
B-NHL phase II adjuvant post-ABMT	CD19	Anti-B4-bR	49	Continuous IV × 7 days every 14 days	210 µg/IBM	Transaminase elevations, thrombocytopenia, VLS	23	27 relapse-free, median F/U 38 months	29
B-NHL phase III adjuvant post-ABMT	CD19	Anti-B4-bR	157	Continuous IV × 7 days every 7 days	210 µg/IBM	VLS, thrombocytopenia, fatigue, dyspnea	NA	No difference between anti-B4-bR and control	129
AIDS-NHL, relapsed	CD19	Anti-B4-bR	9	Continuous IV × 28 days	560 µg/kg	Transaminase elevations	3/9	1 CR, 1 PR	130
AIDS-NHL, previously untreated	CD19	Anti-B4-bR	28	Low-dose in-BACCD + continuous IV × 7 days with cycles 3 ± 4	20 µg/kg/d	Transaminase elevations, fever, myalgia, fatigue	8/28	14 CR, 12 PR, median overall survival 9.1 months	131
B-CLL	CD5	Anti-T101-K1A	9	IV bolus over 1 hour twice weekly × 4 weeks	24-112 mg/m <sup>2</sup>	Fever, nausea, rash	1/9	Rapid, transient decrease in WBC	117, 132
NHL, relapsed	CD25	DAB <sub>388</sub> IL-2	18	IV bolus day 1, 3-5, 14-20	0.1 mg/kg/day	Transaminase elevations, fever, dyspnea, rash	7/18	1 CR, 2 PR, lasting 5 to 18 months	133
NHL, Hodgkin's, CLL, relapsed	CD25	DAB <sub>388</sub> IL-2	15	IV bolus over 30-60 minutes daily × 5 days	0.2 mg/kg/d	Transaminase elevations, hypocalcemia, rash, fever, flank/chest pain, cardiac ischemia	6/14	1 CR in patient with Hodgkin's lasting > 2 years	102
NHL	CD25	DAB <sub>388</sub> IL-2	23	IV bolus over 90 minutes daily × 5 days	0.3 mg/kg/d	Renal insufficiency, hemolysis, thrombocytopenia	15/20	2 PR	134
Hodgkin's relapsed	CD25	RFT5-SMTP-dgA	25	IV bolus over 4 hours on day 1, 3, 5, 7 × 1-4 cycles	5-20 mg/m <sup>2</sup> per cycle	VLS, hypersensitivity, myalgias	7/15	2 PR	135, 136



CD25+ malignancy	CD25	Anti-Tac(Fv)-PE38 (LM8-1)	22	IV bolus, day 1, 3, 5	Up to 40 µg/kg/dose	Transaminase elevations, VLS, fever, thrombocytopenia	3/22	2 PR ( hairy-cell and CTCL)	137
B-ALL	CD19	B43-poleweed antiviral protein	17	Continuous IV × 5 days for 1 or 3 cycles	1.25 mg/kg	VLS, myalgias	0	4 CR, 1 PR	138
Hodgkin's, relapsed	CD30	BerH2-saporin	12	IV bolus over 3 hours day 1-7	0.4 mg/kg/d	Fever, fatigue, mild thrombocytopenia, transaminase elevation, VLS	12/12	8 PR, lasting 6 weeks to 4 months	139, 140
T-Cell CTCL	CD5	Anti-H65-RTA	14	IV bolus daily × 10 days	0.33 mg/kg/d	Fever, chills, nausea, fatigue, VLS	10/14	4 PR, lasting 3 to 8 months	141
Advanced CTCL with Sezary syndrome	CD25	DAB <sub>486</sub> IL-2	14	IV bolus over 90 minutes × 5 days every 21 days	0.2 mg/kg/d	Reversible transaminase elevations	8	1 PR	142
Mycosis fungoides, relapsed	CD25	DAB <sub>486</sub> IL-2	71	IV bolus, daily × 5 days every 21 days, up to 11 cycles	9 or 18 µg/kg/day	Constitutional symptoms, VLS, rash, infections, transaminase elevations	70	CR 3, PR 18, with median response duration 5 months	143, 144
T-NHL, T-LGL	CD7	Anti-CD7-dgA	11	IV bolus over 1 hour × 5 days	0.2 mg/kg/d	VLS, aphasia	1/11	2 PR	145

Abbreviations: LGL, large granular lymphocyte lymphoma; VLS, vascular leak syndrome; MIT, maximum-tolerated dose; HARA, human antihuman antibodies; ABMT, autologous bone marrow transplant; m-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexmethasone; LBM, lean body mass; F/U, follow-up.

\*Only complete and partial responses are reported.

in the 10% to 25% range. The DAB<sub>486</sub>IL-1 fusion toxin similarly had limited activity in both NHL and Hodgkin's disease.<sup>102,103,134</sup> Poor penetration into sites of bulky disease has been the explanation offered for these low response rates.<sup>19</sup> The use of ITs to treat leukemia has been equally disappointing, despite the broad array of conjugates that have been tested.<sup>19,138,145,147</sup> These agents fail to show durable efficacy, mainly for the pharmacologic reasons cited earlier. Most trials document a decrease in the number of circulating tumor cells, which return once the IT has been cleared from the circulation.

The minimal disease state would appear to be the optimal setting for IT therapy. Only anti-B4-bR has been tested in the adjuvant setting, in patients with NHL who attained a CR after high-dose chemotherapy and bone marrow transplantation.<sup>29,30,148</sup> Initial phase I and II pilot trials appeared to show improved disease-free survival over historic controls, but a subsequent randomized phase III trial could show no benefit with respect to relapse-free or overall survival among the patients treated with anti-B4-bR.<sup>129</sup>

Future directions in IT research include the search for less immunogenic toxins<sup>149-151</sup> and toxins that act at the cell surface,<sup>152,153</sup> which obviates the need for internalization. The use of nonprotein toxins is also being explored. Preclinical and early clinical studies have been conducted with the maytansinoids<sup>154-156</sup> and the calicheamicins,<sup>157-160</sup> which are two to three orders of magnitude more potent than conventional chemotherapeutic drugs.

Finally, these agents may have a role in combination with conventional cytotoxic chemotherapy. Preclinical in vitro and in vivo data show synergy between the two modalities.<sup>161-165</sup> Limited clinical trials show that ITs can be administered safely in conjunction with chemotherapy, but it has been difficult to show enhanced cytotoxicity in the absence of a phase III trial.

In summary, the present generation of ITs possess limited clinical activity. Many of the same obstacles encountered with the unconjugated MoAbs also appear to undermine IT efficacy. The main unique obstacle, however, is the toxicity associated with these agents. Although in most cases, side-effects have been tolerable, the vascular leak syndrome may prevent the administration of an adequate quantity of IT. Host immune responses to the MoAb and protein toxin moieties further limit the clinical use of these agents. It is therefore difficult to be sanguine about the prospects for future IT development. Whereas these agents offer the potential to deliver cytotoxic toxins specifically to the malignant cell, they lack the ease of use and low side-effect profile of the unconjugated MoAbs, as well as the ability to kill bystander cells offered by RICs.

## RADIOIMMUNOCONJUGATES

RICs consist of a radionuclide coupled to an MoAb, with the intent of selectively delivering ionizing radiation to tumor cells. Hematologic malignancies are ideal candidates for such a treatment approach because of their exquisite radiation sensitivity. Although many of the same issues that must be considered in the design of unconjugated MoAb and IT therapies also apply to RIC therapies, these agents offer some distinct advantages.

The two major radionuclides used in RIC synthesis,  $^{131}\text{I}$  and  $^{90}\text{Y}$ , emit  $\beta^-$  particles (electrons).<sup>166</sup> Thus, these agents can induce lethal DNA damage at a distance and kill not only antigen-positive cells, but also neighboring cells that may not express the target antigen<sup>167</sup> or that may be physically inaccessible. Furthermore, RICs do not rely on host effector mechanisms or on antigen internalization and cytoplasmic access to mediate cytotoxicity, factors that limit the potency of unconjugated MoAbs and ITs. Nevertheless, similar obstacles must still be surmounted before RIC therapies become feasible. Among these are nonspecific binding by normal host tissues, which contributes to toxicity, and the presence of shed antigen, circulating tumor cells, or large tumor bulk, which depletes the quantity of RIC available to penetrate into other sites of disease.

Although  $^{131}\text{I}$  and  $^{90}\text{Y}$  both emit  $\beta^-$  particles,  $^{90}\text{Y}$  emits higher energy particles, which have a longer mean path length (5 mm v 0.8 mm) and thus deeper tissue penetration.  $^{131}\text{I}$  also emits a high degree of  $\gamma$  radiation and has a half-life of 193 hours, whereas  $^{90}\text{Y}$  has no concomitant  $\gamma$  emission and has a considerably shorter half-life of 64 hours. Thus  $^{90}\text{Y}$  has the theoretic advantage of delivering higher radiation doses in a more homogenous distribution. The short half-life and absence of  $\gamma$  emissions with  $^{90}\text{Y}$ -based RICs also permit outpatient therapy, whereas  $^{131}\text{I}$ -based RICs previously were administered in the inpatient setting under strict radiation isolation. Newer Nuclear Regulatory Commission regulations will relax this requirement.

Most studies of RIC therapy require careful dosimetry measurements with trace-labeled MoAbs before the administration of therapeutic doses to ensure that the radiation doses delivered to all sites of tumor exceed the doses to normal organs. Such biodistribution studies are conducted with gamma imaging cameras after the administration of low doses of radioactivity (5 to 10 mCi), using trace-labeled RIC.<sup>168-174</sup> Only if the biodistribution is deemed favorable can patients receive the pharmacologic dose of RIC. Because patients differ considerably in tumor bulk and location, such dosimetry studies can show strikingly different patterns of predicted radiation exposure.

The distribution, bulk, and total burden of tumor signifi-

cantly determine dosimetry. Spleen size can be a particular problem that disqualifies more than 80% of the patients with splenomegaly from RIC therapy.<sup>175,176</sup> although more recent studies with the  $^{131}\text{I}$ -LYM-1 RIC suggest that only massive spleens preclude RIC therapy.<sup>177</sup> A large tumor burden can similarly interfere with a favorable distribution of radiation. Press et al,<sup>175,178</sup> using  $^{131}\text{I}$ -labeled anti-CD20 and anti-CD37 RICs, found that dosimetry studies were favorable almost exclusively in patients with a total tumor burden of less than 500 g. In an attempt to improve biodistribution, many studies have administered cold or unlabeled MoAbs before the dose of RIC.<sup>179-181</sup> This maneuver presumably saturates the Fc receptors of reticuloendothelial cells, which minimizes nonspecific binding to normal tissues and thus improves the therapeutic index. Whether it also enhances cytotoxicity is unknown.

RICs also present radiation safety concerns. The requirement for an onsite radiopharmacy and dosimetry calculations may limit the application of this approach to a small number of centers. In contrast to unconjugated MoAbs and ITs, RICs have the additional toxicity of myelosuppression, which has uniformly been the DLT in phase I trials, although there is considerable interpatient variability in the depth and duration of the neutrophil and platelet nadirs.<sup>182</sup> In general, the peripheral counts nadir at approximately 3 to 4 weeks and can remain low for as long as 16 weeks posttreatment before full recovery.<sup>179,183,184</sup> Higher doses of radioactivity generally result in a more rapid, deeper, and prolonged nadir. Other factors, such as prior radiation therapy and cytotoxic chemotherapy, also affect the degree of myelosuppression. One factor specific to RIC therapy is bone marrow involvement by tumor and its correlation with toxicity. Extensive bone marrow involvement can lead to greater binding of RIC at this site and a larger radiation dose delivered to the normal marrow hematopoietic elements.

At higher doses of RIC with stem-cell support, cardiopulmonary toxicity may be dose limiting. A phase I trial conducted by Press et al<sup>178</sup> achieved DLT after one patient developed hemorrhagic pneumonitis and congestive cardiomyopathy and another patient developed hypotension that required pressor support. At nonmyeloablative doses, however, RIC therapy has few other systemic or organ-specific toxicities. As with unconjugated MoAbs and ITs, the infusion of RIC can be associated with acute systemic side effects, such as fever, chills, rash, and nausea.<sup>178,184-186</sup> The use of iodine conjugates can cause hypothyroidism,<sup>175,178,187</sup> although pretreatment with unlabeled iodine to limit the uptake of  $^{131}\text{I}$  by the thyroid may decrease the risk. Finally, as with other murine MoAbs, RICs also stimulate HAMA responses in about 15% to 25% of the patients.<sup>32,171,175,187,188</sup>

Re-treatment may be possible, however, in patients who remain HAMA negative after an initial course of therapy.<sup>189</sup>

Some RICs are now synthesized with humanized MoAbs, which should minimize host immune responses.<sup>190</sup> The altered pharmacokinetics of these agents, however, have made investigators reluctant to embrace them. Their prolonged serum half-life increases radiation exposure to normal tissues and thus decreases therapeutic index. Thus, even when humanized MoAbs against a given antigen target are available, most researchers have chosen to continue to use the murine form.

Table 3 lists the major clinical trials published to date of RIC therapy for hematologic malignancies. Two trials have used radiolabeled polyclonal antiferritin antibodies in the treatment of patients with refractory ferritin-rich tumors, such as Hodgkin's disease.<sup>199,200</sup> Subsequent trials have used MoAb-radioisotope conjugates exclusively, targeted against hematopoietic surface antigens.

The trials of nonmyeloablative RIC therapy in NHL have reported high response rates despite the enrollment of patients with relapsed or refractory disease, which included some patients in whom prior bone marrow transplantation failed. The <sup>131</sup>I conjugates that target a number of antigens, which include HLA-DR,<sup>188,195</sup> CD20,<sup>171,172,209</sup> CD21,<sup>187</sup> and CD22<sup>190,196</sup> have achieved complete or partial remissions in 6% to 79% of the patients; most studies reported a 20% to 30% response rate. Moreover, the response durations in these patients frequently were longer than those achieved with their last chemotherapy regimen,<sup>210</sup> with some patients who continued to live disease free after more than 4 years of follow-up.<sup>209</sup> The one study of <sup>131</sup>I RIC in the upfront setting in 21 patients with low-grade NHL reported a 100% response rate, with 15 CRs that included eight patients with bulky disease.<sup>186,197</sup> Follow-up, however, is limited.

Based on the limited number of studies to date, the <sup>90</sup>Y conjugates also appear to be quite active. Studies of <sup>90</sup>Y RICs composed of the B1 and C2B8 MoAbs, which both target CD20,<sup>179,211</sup> in patients with relapsed or refractory NHL document 70% to 90% response rates. Other <sup>131</sup>I- and <sup>90</sup>Y-based RICs targeted against T-cell antigens, such as CD5<sup>202,203</sup> and CD25,<sup>204</sup> also show marked clinical activity.

Even greater response rates in NHL have been reported in the studies that used myeloablative doses of RIC with stem-cell support.<sup>178,183</sup> One study evaluated 25 patients with relapsed B-cell NHL, of whom 22 showed favorable biodistribution studies. Twenty-one patients were ultimately treated with myeloablative doses of an <sup>131</sup>I-anti-CD20 (B1) murine RIC, followed by re-infusion of purged autologous stem cells. Sixteen patients achieved CRs, with two more partial responses, which translated into progression-free and overall survival rates of 62% and 93%, respectively, at a

median follow-up to 2 years. Toxicity included one septic death, two other severe infections, and one case of reversible cardiomyopathy and interstitial pneumonitis.<sup>175</sup> A more recent study showed that <sup>131</sup>I-anti-B1 could be safely combined with conventional chemotherapy, which consisted of cyclophosphamide and etoposide, with stem-cell support. This phase I/II trial treated 38 patients with relapsed B-cell NHL, and after a median follow-up of 1.5 years, 78% of the patients were progression free.<sup>198</sup>

The limited experience of RICs in the treatment of leukemias has also been impressive, in marked contradistinction to the studies that used ITs and unconjugated MoAbs. Studies have been conducted in both lymphoid<sup>201,203,212</sup> and myeloid<sup>32,205</sup> leukemias, with the latter as part of a high-dose chemotherapy regimen with stem-cell support. The largest study, which consisted of 44 patients with AML, myelodysplastic syndrome (MDS), or ALL, reported approximately a 45% CR rate using an anti-CD45 <sup>131</sup>I-conjugated RIC in combination with chemotherapy, total-body irradiation, and allogeneic or autologous stem-cell support.<sup>207,208</sup> Further work remains to be done to confirm these initial encouraging findings.

Research into improving the efficacy and therapeutic index of RIC therapy is proceeding along several lines. Repeated fractionated dosing instead of single large bolus dosing may be more active with reduced toxicity,<sup>213,214</sup> although HAMA formation could conceivably limit repeated dosing. Recent *in vitro* evidence also suggests that RICs may be synergistic with certain chemotherapeutic agents, particularly the nucleoside analogs and topoisomerase inhibitors.<sup>215</sup> The use of alpha-emitting radioisotopes, such as bismuth-212 and bismuth-213, also may increase RIC potency because of their ability to deliver higher energy particles over shorter distances, on the order of 10 to 80  $\mu$ m. Such RICs would be two to three orders of magnitude more cytotoxic than conventional  $\beta$ -emitter-based RICs.<sup>216,217</sup>

RICs show great potential for the treatment of hematologic malignancies. Although the most cumbersome of the MoAb-based therapies, they offer marked activity at nonmyeloablative doses, even in the relapsed or refractory disease setting. The question remains whether RICs offer any advantage over conventional total-lymphoid irradiation when they are administered at less than myeloablative doses. Furthermore, although the toxicity profile generally is predictable and tolerable, particularly with modern dosimetric techniques, it is too early to comment on long-term toxicities that may be associated with the irradiation of hematopoietic stem cells, such as MDS.

Optimized dosing schedules and more potent radionuclides promise to increase the safety and efficacy of these agents. Finally, RICs may become an integral part of

Table 3. Major Studies of Radioimmunconjugates

Disease	Target Antigen	Antibody	Dose (mg)	Isotope (dose mCi)	No.	Response*	Toxicity	HAMA	Reference
Lymphoid	CD20	B1	58-1,168	<sup>131</sup> I [280-777]	29	23 CR, 4 PR	Severe myelosuppression, requiring autologous bone marrow rescue in 24/28 patients,	1/9	178, 183, 191
	CD20	1F5	274	<sup>131</sup> I [608]	1	1 PR		0	
	CD37	M81	275-970	<sup>131</sup> I [234-628]	6	6 CR		3	
	Ig	Anti-Ig	1,000	<sup>131</sup> I [232]	1	1 CR	nausea, elevated TSH	0	
B-NHL, relapsed	HLA-DR	LYM-1	8-676	<sup>131</sup> I [26-1,044 in 1-16 courses]	57	11 CR, 20 PR	Myelosuppression, fever, rash, nausea, hypotension	3/18	188, 192-194
B-NHL, relapsed	HLA-DR	LYM-1	30-67	<sup>131</sup> I [50-267 in 1-2 doses]	13	4 PR	Myelosuppression, fever, nausea, pruritis, chest pain, bronchospasm	3	195
B-NHL	CD21	OKB7	25	<sup>131</sup> I [90-200 in 3-4 doses]	18	1 PR	Myelosuppression, asymptomatic elevation of TSH	12/16	187
B-NHL, relapsed	CD22	LL2	2.1-7.3	<sup>131</sup> I [31-102 in 1-3 doses]	7	2 PR	Myelosuppression	3	196
B-NHL, relapsed	CD22	LL2	1.1 of IgG to 1.57 of F(ab') <sub>2</sub>	<sup>131</sup> I [15-343 in up to 7 doses of 15-50 per dose]	21	2 CR, 2 PR of 17 assessable	Myelosuppression	8/19	190
B-NHL, relapsed	CD22	LL2	100 mg IgG	<sup>131</sup> I [90/m <sup>2</sup> ], myeloblastic with ABMT	3	2 PR of 2 assessable, lasting 3 and 8 months	Myelosuppression	NA	190
B-NHL, relapsed	CD37	M8-1	40	<sup>131</sup> I [25-161]	10	1 CR, 2 PR, lasting 3 weeks to 6 months	Myelosuppression, fever	2	184
B-NHL	CD20	B1	2.5 mg/kg	<sup>131</sup> I [345-785], myeloblastic with purged autologous stem cells	25	16 CR, 2 PR of 18 assessable	Nausea, mild mucositis, asymptomatic elevation of TSH, reversible cardiomyopathy and interstitial pneumonitis in 1 patient	4/25	175
B-NHL, relapsed	CD20	B1	15-20	<sup>131</sup> I [34-161]	59	20 CR, 22 PR with median response duration of 271 days	Mild leukopenia and thrombocytopenia, fever, nausea, asthenia, chills	9	171, 172
B-NHL, low-grade, previously untreated	CD20	B1	35-50	<sup>131</sup> I [58-142]	21	15 CR, 6 PR including 8 of 13 patients with bulky disease	Myelosuppression, fever, headache, pruritis, myalgias, and arthralgias	7	186, 197
B-NHL, relapsed	CD20	B1	2.5 mg/kg	<sup>131</sup> I [318-840] + CTX [100 mg/kg] ± ETP (60 mg/kg) with ABMT or PBSC	38	78% progression-free after median F/U of 1.5 years with 37 assessable patients	4 deaths (3 progressive disease, 1 infectious), myelosuppression, nausea, pulmonary infiltrates, venoocclusive disease	NA	198

B-NHL, relapsed	CD20	BI or CZ88	10.3-13.5 mCi/mg	<sup>90</sup> Y (13.5-53.4 in 1-2 doses)	18	6 CR, 7 PR	Myelosuppression (2 patients required stem cell support at the highest dose level), fever, infection	4	179
Lymphoid B-NHL	Ig	Anti-Id	< 2	<sup>90</sup> Y (10-54 in 1-4 cycles)	9	2 CR, 1 PR	Myelosuppression, transient hypotension	0	173
B-NHL, relapsed	HLA-DR	LYM-1	135-288	Cu-67 (131-388 in 1-4 doses)	3	1 CR, 1 PR			193
Hodgkin's relapsed		Anti-feritin	3-10	<sup>131</sup> I (50-100 in 1-2 doses)	37	1 CR, 14 PR	Thrombocytopenia, neutropenia	0	199
Hodgkin's, relapsed		Anti-feritin	1-5	<sup>90</sup> Y (20-80 in 1-3 doses)	37	9 CR, 9 PR	17 Received bone marrow rescue, 3 died of aplasia and 1 of pulmonary fibrosis	NA	200
CLL	CD5	T101	5-10	<sup>125</sup> I (25-50)	4	No responses	Fever, pruritis	—	201
CTCL	CD5	T101	10-16	<sup>125</sup> I (100-150)	6	2 PR	Myelosuppression, fever, pruritis, dyspnea	6	202
CLL, CTCL	CD5	T101	NA	<sup>90</sup> Y (NA)	6	3 PR	NA	2	203
T-ALL/NHL, both previously untreated and relapsed	CD25	Anti-TAC	2-10 per dose	<sup>90</sup> Y (5-66 in 1-9 doses of 5-15 per dose)	18	2 CR, 7 PR of 16 assessable	Myelosuppression	6/15	204
Myeloid AML	CD33	P67.6	4.3-9.2	<sup>125</sup> I (110-330) + CTX (120 mg/kg) + TBI (12 Gy) with ABMT	4	4 CR	Myelosuppression	1	205
AML and MDS	CD33	M195	NA	<sup>125</sup> I (50-210/m <sup>2</sup> )	24	3 CR	Myelosuppression (8 patients received bone marrow support), hepatic toxicity (in one patient)	7/19	32, 206
AML, MDS, and ALL, relapsed	CD45	BC8	NA	<sup>125</sup> I (76-612) + CTX (120 mg/kg) and TBI (12 Gy) with allogeneic or ABMT	44	15 CR (12 with AML/MDS and 3 with ALL)	Myelosuppression, mucositis, vasoocclusive disease	NA	207, 208

Abbreviations: PBSCT, peripheral blood stem-cell transplant; CTX, cyclophosphamide; ETP, etoposide; Cu-67, Copper-67; MDS, myelodysplastic syndrome; TBI, total-body irradiation; TSH, thyroid-stimulating hormone.

\*Only complete and partial responses are reported.

myeloablative combination chemotherapy regimens, perhaps augmenting or replacing total-body irradiation. More studies need to be conducted to fulfill this promise, but the prospects are enticing.

In conclusion, the development of MoAb-based therapies has encountered many unforeseen complications, which belies the simplicity of the original concept. Nevertheless, antibody-based therapies continue to hold promise for the targeted treatment of hematologic malignancies. The low toxicity and ease of use make unconjugated MoAbs an attractive modality that permits low-risk outpatient treatment with minimal investment of resources.

The best role for unconjugated MoAbs remains to be determined. Although they show activity as single agents, they may eventually have a greater role in conjunction with conventional cytotoxic chemotherapy or in the minimal disease setting, in which the problems of tumor bulk and circulating disease can be avoided. Maintenance therapy may be another possible use for these agents, although antigen mutation or modulation may limit repetitive administration. The RICs stand at the opposite end of the spectrum and offer significant efficacy but at the cost of toxicity.

Newer dosimetric techniques have improved the ability to predict toxicity, but some degree of myelosuppression cannot be avoided. In addition, only large clinical centers may have the institutional resources to deliver this modality.

The development of ITs had perhaps the most unexpected complications, despite a simple conceptual basis. At its best, the efficacy of the current generation of ITs approximates that of unconjugated MoAbs but with added toxicity. The next generation of toxin conjugates, which use new toxins and humanized MoAbs, may improve the therapeutic index and potency of these agents, but for now, ITs appear to be the furthest of all the MoAb-based therapies from general clinical use.

Thus MoAb-based therapies may have important roles at many phases in the care of the patient with a hematologic malignancy, from initial treatment through relapse and into stem-cell transplant. In each of these settings, a different MoAb-based modality may be used. Much of the work to show the feasibility of delivering these therapies safely has been completed, but considerable work still remains to optimize efficacy and define appropriate uses.

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